REMARKS

Claims 1-20 are pending in the application. Claims 1, 18 and 20 are currently amended. Claims 8, 9, 19, and 20 are allowed.

Claim 1 is amended to recite "two direct repeats of a gene of interest which are capable of recombination with the genome of the host cells, said direct repeats immediately flanking the positive and negative selectable marker genes." This amendment finds support, for example, in example 3 beginning on page 14 of the Specification, Figs. 1A and 1B, and other places in the Specification. Amendment to claim 18 is made to correct a dependancy and provide proper antecedent. The amendment to claim 20 corrects a typographical error with respect to the word "is."

I. Rejections under 35 U.S.C. 112, 2nd Paragraph

The amendment to claim 18 is made to correct the dependancy of this claim, which formerly depended from claim 4 and now depends from claim 17. This amendment should overcome the rejection under 35 U.S.C. 112 second paragraph.

II. Rejections under 35 U.S.C. 102(e)

Claims 1 and 4 stand rejected under 35 U.S.C. 102(e) as being anticipated by Bauer et al. U.S. Patent 6,534,315. As amended, Claims 1 and 4 are patentably distinct from Bauer. First, the direct repeat sequences (DRSs) immediately flanking the selective markers in the present invention differ from the DRSs in Bauer. The DNA cassette disclosed in Bauer for the transformation of yeast comprises at least one negative marker, *two direct repeat sequences (DRS) which are non-exogenous and non-recombinogenic with the genome of the host strain* (See Abstract of the '315 patent, emphasis added). Exhibit I accompanying provides a graphical illustration of the claimed distinction. The DNA cassettes of Bauer and the constructs that are presently claimed both contain two direct repeat sequences (DRS) that immediately flank the positive marker (PS) and negative marker (NS); however, there is a significant difference. The DRSs in Bauer must be non-recombinogenic; i.e., these sequences are designed so that they do not recombine with the genome of the host cells (See Abstract and lines 4-7 of column 4 of the '315 patent). By contrast, the DRSs that are presently claimed are direct repeats of the gene of interest, and can mediate the integration of the entire DNA construct into the host genome by recombination (*See e.g.*, paragraph 48 of the present application).

The claimed distinction has advantages that are disclosed in the present Specification. The DRS in Bauer is non-coding (lines 42-48 of column 4), while the DRS in the present claims can be coding (See paragraphs 36 and 37). Also, the sequences mediating insertion of the DNA constructs into the host genome may differ from those disclosed in Bauer. Recombination may be random insertion mediated by the presently claimed DRSs, which may include nucleic acids encoding viral, parasitic, tumor, bacterial, or other known immunogens (See paragraph 37 of present application). In contrast,

the '315 patent teaches recombinogenic sequences (RS—not the DRS) which correspond to the desired insertion site in yeast (lines 8-10, column 4 of '315 patent). For instance, Figure 12 and Example 4 describe a CAS-SUC cassette in which the RSs are chosen from a region present in all the SUC loci so that the double homologous recombination leading to the integration of the cassette can take place in any SUC locus of the genome (Fig. 12 and lines 19-23 of column 19 of '315 patent). Thus, while the RSs in Bauer mediate insertion of the DNA cassette into the host genome exclusively through homologous recombination, the DRSs in the present invention may mediate integration of the cassette through non-homologous random recombination.

The DNA that is left on the host chromosomes as a result of the integration and excision events according to the present claims also differs from Bauer. The DNA constructs and the methods taught in Bauer generally leave behind the gene of interest as well as a non-exogenous DRS which usually comes from an organism belonging to different species from the host organism (See lines 59-63 of column 3 and lines 35-40 of column 4). In contrast, according to the present claims, only one copy of the gene of interest is left on the host chromosome after successful integration/excision (paragraph 21 of present application).

Therefore, the present claims are not anticipated by Bauer because the genetic constructs and methods of Bauer do not teach or suggest the limitations of the present claims. Applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C. 102(e).

III. Rejections under 35 U.S.C. 103 over Bauer

Claims 1, 6, 10, 12, 14 and 15 stand rejected under 103(a) as being obvious over Bauer et al. Applicants respectfully traverse for the following two reasons: First, there is no suggestion or motivation in Bauer or in knowledge generally available to one of ordinary skill to modify the constructs and methods taught by Bauer. The Examiner appeared to base the rejections on the assumption that the present invention differs from Bauer merely in the arrangement of the positive and negative markers within the construct and in the presence or absence of additional genes. Applicants respectfully disagree because, as discussed in Section II above, the constructs and methods claimed in the instant application differ from those disclosed in Bauer in many aspects. Bauer disclosed two RSs at either end of the DNA cassette which have substantial sequence similarity to the host yeast genome (see lines 13-17 of column 2 and lines 8-10 of column 4). Indeed, Bauer's principle of operation entails homologous recombination through these RSs. By contrast, homologous recombination is not required for the present invention to be operable, and so a distinct advantage is gained. Indeed, to modify Bauer to arrive at the present claims would change the principle of operation in Bauer. Bauer teaches away from the present claims by requiring non-recombinogenic DNA precisely at the site where recombinogenic sequences are now claimed. Therefore, Bauer's teachings are not sufficient to render the present claims *prima facie* obvious.

Secondly, the Bauer reference does not teach or suggest all the limitations of the present claims. Claim 1 of the instant application as amended recites "two direct repeats of a gene of interest..." The claimed construct requires two identical copies of the same gene of interest to be placed immediately flanking the selective markers. In contrast, the gene of interest is placed between the DRS and the RS as a single copy (see Exhibit I). While the two direct repeats of the gene of interest in the present invention help mediate subsequent recombinations, the single copy of the gene of interest does not play any significant role in the recombination event. Thus, not only are the constructs of the present application and Bauer different in structural arrangement, but the functionalities associated with each arrangement also vary significantly. Therefore, the present claims are not rendered obvious by Bauer and Applicants respectfully request that the Examiner withdraw the 103(a) rejections of Claims 1, 6, 10, 12, 14 and 15.

IV. Rejections under 35 U.S.C. 103 over Bauer in view of Ow

Claims 1, 4, 17 and 18 are rejected under 103(a) as being obvious over Bauer et al. and further in view of Ow, D. (WO 93/01283). Applicants respectfully traverse for the same reasons as set forth in Section III above. Ow does not provide any suggestion or motivation to modify Bauer, nor does the combination of Ow and Bauer teach or suggest all the limitations of the present claims as is required to establish a prima facie case of obviousness rejection.

Based upon the foregoing discussion, Applicant's attorney submits that the amended claims are allowable and respectfully solicits a Notice of Allowance. Authorization is given to charge deposit account 12-0600 if any additional fees are due.

Respectfully submitted,

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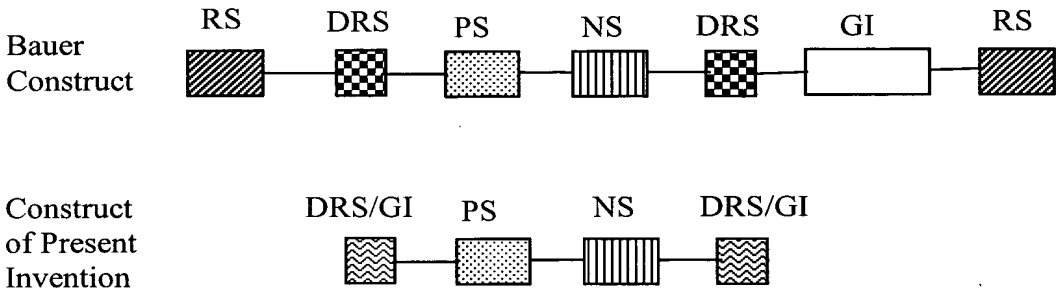
Exhibit I



RS: Recombinogenic Sequence
DRS: Direct Repeat Sequence
PS: Positive Selectable Marker
NS: Negative Selectable Marker
GI: Gene of Interest